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ON THE DEVELOPMENT OF X-RAY INJURIES TO THE SKIN

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Present-day and historical concepts and directions in the study of the pathological process of X-ray injuries to the skin are summarized, and compared with the author's findings. The article evalutes changes in the afferent side of the reflex arc providing innervation to the irradiated sector of skin (nose & lip of cat). Study conditions and parameters are specified, and changes occurring 10 min to 3 weeks and 2 months after specimen exposure are exhaustively examined. The author details his disagreement with most investigators that radiation damage to skin consists of selective injury of vessel walls by radiation energy.

Radiation injuries of the skin have been studied since X-rays were /332* discovered. Thanks to numerous investigations, the clinical course and general pathomorphological and pathophysiological characteristics of these injuries are well known. However, questions concerning the effect of ionizing radiation on the skin continue to occupy the center of attention of investigators at the present time. This is because radiation injuries of the skin still remain one of the most severe and often least tractable injuries encountered in clinical practice, so that problems of the pathogenesis and therapy of this type of injury require further study in depth.

At present there is no unanimous viewpoint concerning the essential features of the pathological process in these injuries. The most popular view is that they are basically due to severe and selective radiant energy damage /333 to blood vessel walls, accompanied by the development of obliterating endarteritis and telangiectasis (O. H. Petersen and J. Hellmann, 1920; Leu, 1949; H. A. Telon, Mason and M. Zan Wheclock, 1950).

However, a study of the literature shows that these changes in vessel walls generally appear only after a considerable lapse of time, often many years after exposure. The acute period of development of skin lesions (Fahr, 1925; J. Mieschen, 1925, 1928) usually passes without any serious changes in vessel walls. During this period various circulatory disturbances are noted in the irradiated sector of skin, which David and Gabriel (1924) attribute to injuries of vasomotor nerves. There exist a number of other papers affirming the appearance of definite nervous system disturbances in irradiated skin. Until the present, however, no supporting facts demonstrating the participation of the nervous system in the development of lesions in skin exposed to X-rays have

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*Numbers given in margin indicate pagination in original foreign text.

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been presented. Some studies are known which deal with changes in neural formations in skin injured by radiation (M.S. Lyutershteyn and A.V. Rakhmanov, 1926; M.N. Maysel', 1930; V.A. Bashinskaya, 1938; et al.). In some, actual changes in neural structures in irradiated areas of the skin have even been detected. Unfortunately, however, their significance in the development of radiation injuries of the skin has not been demonstrated.

The purpose of our study was to follow the appearance and development of changes in the afferent side of the reflex arc providing innervation to the irradiated sector of skin, and to determine the significance of these changes in the development of the total tissue reaction in the irradiated part.

The most suitable object was the skin of the end of the nose and upper lip, whose sensitive innervation is provided chiefly by tendrils of the second branch of the trigeminal nerve. All the receptors in this area of the skin are axon tendrils of sensitive neurons which are concentrated in the gasserian ganglion of the trigeminal nerve.

To eliminate the effect of direct exposure to ionizing radiation on the above-mentioned nerve centers and to limit the effect of radiant energy to a small sector of skin, irradiation was done on a "Dermamobile" apparatus with soft X-rays having a maximum tissue penetration depth of 4 mm. Irradiation conditions were: voltage, 30 kV; power, 25 mA; filter, 1 mm Al; skin focal distance, 10 cm; dose power, 400 R/min. In all cases, single exposures were used; doses were 3000 and 5000 R, and the irradiation field diameter was 1.5 cm.

A total of 57 male cats were irradiated. Ten animals, healthy for practical purposes, served as controls. The condition of receptors in the irradiated sector of skin, and of their trophic centers in the gasserian ganglion which was not directly exposed to radiant energy, was studied. In addition, other sensitive nodes in the Ganglion nodosum of the vagus nerve and sensitive spinal ganglia in the cervical portion of the spinal cord were studied. Material for histological study was taken at various periods after irradiation (from 10 min to 4 months) and was studied by various cytological and neurohistological methods. Fresh skin specimens taken from 10 min to 3 weeks after exposure were also processed using our modification of Gomori's method to show up acid and basic phosphomonoesterases.

Vasodilation was noted in the irradiated sector of skin in the first 1 to 2 hr after irradiation, disappearing toward the beginning of the 3d hr. During the first 3 days after irradiation, no substantial changes in the structure of the skin were noted. The sole change, which is highly characteristic, was the appearance of a large number of plasmacytes in the connective tissue lay- /334
ers of the skin. Although nerve fibers and sheaths in specimens treated by conventional methods did not differ from those from control animals, the specimens treated to bring out phosphomonoesterases showed changes in enzyme activity in the vicinity of the sensitive neural formations of the skin within the first 10 min after irradiation. Basic phosphatase activity, determined in the Schwann symplast of the inner bulb in receptors and in the sheath of pulpy fibers, was found to increase, while acid phosphatase activity, detected in axial cylinder structures, showed a decrease. By the 3d day, changes in neural

structures could also be seen in the conventionally prepared specimens. The sheaths of myelinized fibers were considerably swollen. Preterminal portions of sensitive nerve fibers showed increased argentophilia and multiple infiltrations of neuroplasm, which causes their outlines to become uneven and jagged. The terminal portions of nerve fibers remained unchanged at this time.

Beginning with the 5th day, changes in the skin became more pronounced, with the pathological process beginning earliest in adventitious tissues. Lesions first appeared in the epidermis. Epithelial cells of the Malpighian layer began to stain much more faintly than normally, and the boundaries between individual cells often tended to lose definition. Large numbers of neutral fat droplets appeared in the protoplasm of many cells. Cell and especially nucleus polymorphism was unusually clearly pronounced; many cells contained from 2 to 4 nuclei apiece. Similar changes were seen in the epithelium of hair follicles and hair bulbs. Degenerative changes were also seen in the salt glands. The sweat glands at this period retained their normal structure.

In the connective tissue layer, just as earlier, many plasmacytes were seen near the vessels. In the papillary layer of the skin, usually in those parts where the epidermis was most changed, there was a considerable increase in young connective tissue cells. Collagen fibers seemed somewhat swollen. At this time the first changes in the vessels were seen: their lumina were dilated, although the arterial lumina seem somewhat constricted due to swelling of their walls. These vascular changes became steadily more severe right up to the appearance of prestatic states and capillary stasis. In parts of the skin containing adventitia, similar changes appear considerably later, on the 10th to 14th day.

Sensitive nerve endings and fibers showed considerable changes during the epidermal degeneration period. In the preterminal portion, coarse argentophilic segments heavily infiltrated with neuroplasm alternated in the fibers with abnormally thin, wasted, weakly staining segments. Later these fibers disintegrated. The terminal portion did not decompose, but became very thin and stained poorly.

In the capillary layer of the skin towards the 14th day, and in those parts of the skin lacking adventitia towards the end of the 3d week, the process of degeneration of the epidermis and skin adventitia was so far advanced that generally enlarged foci of necrosis were forming. It is interesting to note that leukocytic infiltration of the skin was not seen at all until the formation of necrotic foci. As soon as necrotic areas appeared in the epidermis and skin adventitia, copious exudation of leukocytes commenced and the entire area of necrosis appeared infiltrated by them.

In the necrotis areas, typical sensitive endings could no longer be discerned. Only individual thin fragments of fibers and disintegrating nerve stems were visible. In encapsulated neural formations, along with degeneration and decomposition of fibrillar structures, necrotization of inner /335
bulb Schwann symplasts could be seen. In the large nerve stems of the deep plexus of the skin, decomposition and degeneration of fibers were not seen.

All changes in the neural formations were limited to their terminal and pre-terminal zones.

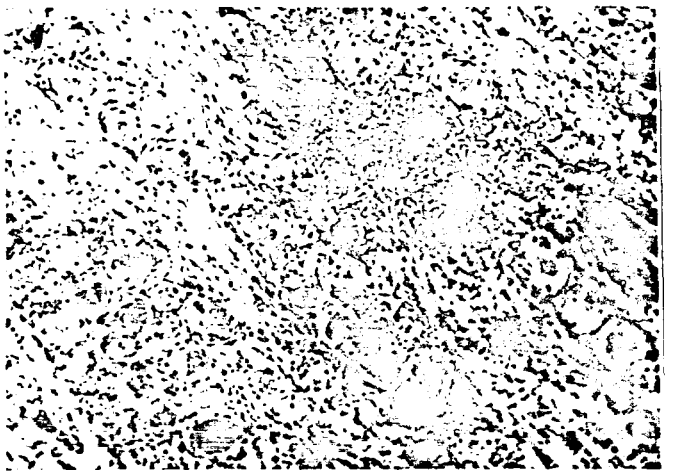
The acute period of injury ended with evulsion of necrotized masses and reepithelialization of the sectors of skin thus exposed. Regeneration did not include the development of fibrous tissue. In the capillary layer this process was complete toward the end of the 3d week, and in the parts of the skin not containing adventitia, towards the end of the 4th week.

However, normal skin structure was not restored. The epidermis, initially subject to hyperplasia, gradually atrophied; the papilla coalesced and hair and salt glands were entirely lacking. The sweat glands also atrophied, probably due to the obliteration of their drainage ducts. Skin which had undergone these changes appeared thin, pale and dry. At this time substantial changes in the walls of blood vessels still could not be observed. Only the persistent dilation of the lumen in veins and the formation of a peculiar sleeve or collar of plasmacytes around some arteries were noted. Along with these changes, there was a great reduction in the number of sensitive nervous formations in the skin. There were almost no encapsulated endings, and the free endings presented only thin fibers with numerous varicosities. Fairly often these fibers were seen to be decomposed.

Thus, at this period of the development of radiation injuries of the skin, definite structural deficiencies of the skin's sensitive neural apparatus were observed.

Two months after exposure to radiant energy without other trauma of any sort, a new wave of changes in the epidermis of the already atrophied skin was observed: foci of necrosis and a copious leukocytic reaction. In the necrotic areas, which were much smaller than those which appeared in the initial lesion period, there appeared disintegration or severe degeneration of all sensitive neural formations. In areas of skin untouched by necrosis, the majority of sensitive neural formations also underwent degenerative changes. In the connective tissue layer of the skin, infiltrations of plasmacytes and lymphocytes were frequently observed. Changes in the blood vessels in areas affected by degeneration were analogous to those seen during the first wave of degeneration. Outside these areas, substantial changes in vessel walls were not observed. Not until 4 months after irradiation was it possible to observe an increase in the number of endothelial cells in the inner coating of small arteries, probably a symptom of incipient endarteritis.

Changes were also detected in the gasserian ganglia. In the initial period of skin injury, during the gradual development of degenerative changes in the epidermis and sensitive neural formations, changes in neural elements and in the stroma of gasserian ganglia were not observed. The first changes in the latter were seen accompanying the severe degeneration of epidermis and sensitive neural formations of the skin which occurred beginning with the 2d or 3d week after exposure. Nodules of polyblasts appeared in the stroma of the ganglia (see figure), the tissue of the ganglion sometimes being infiltrated by them. At the same time a fairly large number of neurons showed perinuclear chromatolysis. Later, during the stage of greatest destruction of sensitive



Nodules of polyblasts. Gasserian ganglia of a cat 21 days after irradiation of the skin of the tip of the nose with a 5000-R dose of soft X-rays.

nerve endings in the skin, the reaction in the stroma had already subsided in intensity, but degenerative changes were seen in the nerve cells. Neuron degeneration was either of the vacuole degeneration type, or of the "severe Nissl degeneration" type. Changes of this nature in the ganglia were seen in all cases which we studied from 30 to 120 days after irradiation. Similar /336 changes were not observed in other sensitive ganglia.

As can be seen from the data presented, exposure to radiation is followed by development of a slow process of degeneration of all tissues in the irradiated sector of skin.

On the basis of these results we may conclude that from the very first hours of the development of radiation injury, progressive structural changes arise in the receptor neural formations of the skin which end in the destruction of the majority of receptors. Our data are not yet sufficient to permit us to state that changes in neural structures are the determining factor in the genesis of radiation injury. However, we feel that the dystrophic process which develops on exposure to radiation energy is closely related to disturbances of afferent innervation.

We cannot agree with the opinion of the majority of investigators that in essence radiation damage to the skin consists of selective injury of vessel walls by radiation energy. It is evident from the literature, and confirmed by our data, that the vascular reaction in radiation injuries occurs in two phases. The first phase (prompt erythema) occurs immediately after exposure to radiation energy and is reversible, disappearing in 1 to 3 hrs. The character of this prompt erythema and its extension to normal skin beyond the area exposed to irradiation indicate that the erythema is reflexive in nature. After the first phase there begins a period during which no circulatory

disturbance whatever is seen in the injured area (the so-called latent period). The second phase in our experiments (major erythema) developed on the 5th to 10th day--depending on the skin area--and was steady and progressively more severe. The great resemblance in timing, course, and character between circulatory disturbances seen in local radiation injury and those following afferent nerve resection (Men'shutin, 1944; Dzherakyan, 1944) is noteworthy. We know of no other skin reactions accompanied by hemodynamic disturbances which follow a similar course (frostbite, burns, inflammation, and the like). This resemblance does not provide a basis for stating that the reaction to irradiation is identical with the neurodystrophic process which develops when afferent innervation is impaired. We merely wish to emphasize that serious proofs of the selective effect of radiation energy on blood vessel walls do not exist. On the contrary, on the basis of the date which we obtained on the very prompt and progressive impairment of afferent innervation in the irradiated sector of skin, it may be stated that the vascular reaction may quite possibly be fully accounted for by that impairment.

That there is trauma to the afferent nervous system in radiation injuries, is beyond doubt. This is demonstrated by us and confirmed by the materials of physiological studies. M. N. Livanov and N. S. Delitsina (1953) established that tactile stimulation of the skin during the first week after its exposure to radiation (dose of 5000 R) does not induce bioelectric activity in the appropriate sensitive nerves of the skin. It is interesting to note that the sharp impairment of the activity of the receptors at that period corresponds morphologically to reactive changes. Evidently these morphological changes must be considered rather more serious than was thought earlier.

Although at this stage it is possible to speak only of disruption of function, there later commences a unique form of deafferentation of the irradiated sector of skin. During the latter, M. N. Livanov and N. S. Delitsina observed the appearance of high spontaneous bioelectric activity in the sensitive nerves in the absence of reaction to tactile stimulation. At this time the appearance of morphological changes in the corresponding trophic centers was also observed. This process occurs without the symptoms of increasing degeneration and brings many sensitive neurons to a state of advanced destruction. Evidently changes in the gasserian ganglia occur as a result of functional overloading of their neurons, which are bombarded for long periods with currents of spontaneous impulses. None of the phenomena in the gasserian ganglia are connected with the direct effects of X-rays, which the irradiation method was chosen to avoid, and are therefore secondary effects. The presence of secondary consequent phenomena in the corresponding nerve centers is a characteristic feature of acute radiation injury of the skin. In all probability precisely these phenomena explain the structural deficiencies of the newly formed receptor elements, in which we may see one of the direct causes of the wavelike course of acute radiation injuries of the skin.

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